



Q1 Financial Results Webcast and Conference Call

May 23, 2024

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AGENDA

- 01 OVERVIEW
- 02 VAROGLUTAMSTAT IN KIDNEY DISEASE
- 03 FINANCIAL RESULTS
- 04 OUTLOOK & STRATEGIC PRIORITIES
- 05 Q&A

Recent findings confirm strong kidney function data and reinforce our strategic shift towards inflammatory and fibrotic diseases

Q1 and post-period highlights



- ◆ **VIVIAD kidney analysis** – revealed statistically significant effect on prospectively defined kidney function endpoint (eGFR¹)

Recent findings / activities²

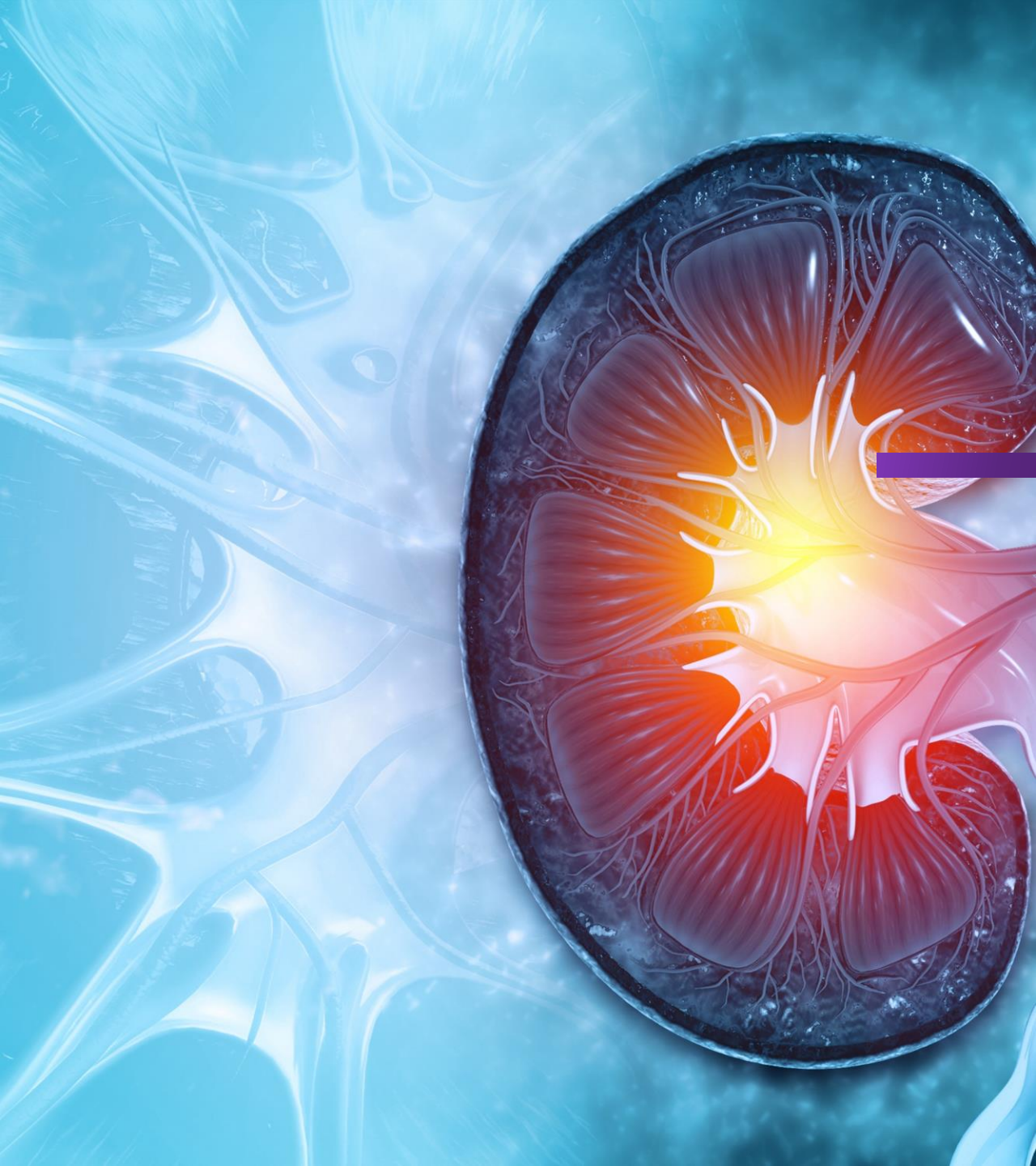
- ◆ Analysis **continues to confirm strong kidney function data** showing significant improvement in eGFR with varoglutamstat 600mg BID in elderly patients with and without risk factors for CKD³
- ◆ Effect is observed across the range of **eGFR levels** at baseline in the study
- ◆ Biomarker results **support anti-inflammatory mechanism** of QPCT/L inhibition



- ◆ **VIVIAD in early AD** – topline data reported in March: study missed primary & secondary endpoints
- ◆ **VIVA-MIND** study being discontinued in H2 2024; stopping VIVALONG study preparations

- ◆ Continued analysis of VIVIAD **shows no consistent effect** on cognition in a subgroup of patients with high CSF drug exposure
- ◆ VIVA-MIND data expected end 2024 to inform next steps





VAROGLUTAMSTAT IN KIDNEY DISEASE

QPCT/L inhibitors and inflammation/fibrosis: Over a decade of research and know-how

Persistent low-grade inflammation is now considered a hallmark feature of chronic kidney disease (CKD)¹

- ◆ Many inflammatory and fibrotic pathways require formation of N-terminal pyro-glutamates (pE) for full activity
- ◆ pE versions of chemokines like CCL-2 and CX3CL1 (fractalkine) are increased in CKD and may contribute to renal diseases^{2,3,4,5}

CCL2 is a validated target in kidney disease

- ◆ QPCT/L inhibition has been shown to improve kidney function and reduce inflammation in a glomerulonephritis CKD rat model via CCL2/CCR2 axis, using a Vivoryon compound⁶
- ◆ CCL2 deficiency protects against chronic renal injury in murine renovascular hypertension⁷
- ◆ Blocking CCL2/CCR2 signaling ameliorates diabetic nephropathy in db/db mice⁸
- ◆ CCL2 plasma levels were significantly higher in patients with CKD compared to the control group⁹



Inhibition of Glutaminyl Cyclases alleviates CCL2-mediated inflammation of non-alcoholic fatty liver disease in mice

Holger Cynis^{1*}, Astrid Kehlen², Monique Haegeler³, Torsten Hoffmann⁴, Ulrich Heiser⁵, Masato Fujii², Yuichiro Shibazaki², Hiroyuki Yoneyama², Stephan Schilling⁶ and Hans-Ulrich Demuth⁶
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INTERNATIONAL JOURNAL OF

SUMMARY

Research Article
100C as drug target in inflammatory disorders

EMBO
Molecul

Research Article

N-terminal pyroglutamate formation in CX3CL1 is essential for its full biologic activity

Astrid Kehlen^{1,2}, Monique Haegeler¹, Livia Böhme^{1,4}, Holger Cynis^{1,3}, Torsten Hoffmann¹ and Hans-Ulrich Demuth^{1,3}

¹Probiolog AG, Weibergweg 22, Halle (Saale) 06120, Germany, ²Institute of Medical Microbiology, Medical School, Martin-Luther-University Halle-Wittenberg, Weinbergweg 22, Halle (Saale) 06120, Germany, ³Department of Drug Design and Target Validation, Fraunhofer Institute for Cell Therapy and Immunology, Weinbergweg 22, Halle 06120, Germany, ⁴Deputy of Research, Medical Faculty, Martin-Luther-University Halle-Wittenberg, Magdeburger Str. 8, Halle (Saale) 06112, Germany
Correspondence: Hans-Ulrich Demuth (hans-ulrich.demuth@izt.fraunhofer.de) or Torsten Hoffmann (torsten.hoffmann@probiolog.de)

The isoenzyme of glutaminyl cyclase is an important regulator of monocyte infiltration under inflammatory conditions

Holger Cynis¹, Torsten Hoffmann¹, Daniel Friedrich¹, Astrid Kehlen¹, Kathrin Gans¹, Martin Kleinschmidt¹, Jens-Ulrich Rahfeld¹, Raik Wolf¹, Michael Wermann¹, Anett Stepha Monique Haegeler¹, Reinhard Sedlmeier², Sigrid Graubner², Wolfgang Jagla², Anke Müller Rico Eichentopf³, Ulrich Heiser³, Franziska Seifert³, Paul H. A. Quax⁴, Margreet R. de Vrie Isabel Hesse⁵, Daniela Trautwein⁵, Ulrich Wollert⁵, Sabine Berg⁶, Ernst-Joachim Freyse⁶, Stephan Schilling^{1*}, Hans-Ulrich Demuth^{1,2}

> *Biochem J.* 2012 Mar 1;442(2):403-12. doi: 10.1042/BJ20110535.

Inhibition of glutaminyl cyclase attenuates cell migration modulated by monocyte chemoattractant proteins

Yi-Ling Chen¹, Kai-Fa Huang, Wen-Chih Kuo, Yan-Chung Lo, Yu-May Lee, Andrew H-J Wang

frontiers
in Immunology

REVIEW
published: 17 June 2013
doi: 10.3389/fimm.2013.00013

Naunyn-Schmiedeberg's Archives of Pharmacology (2021) 394:751-761
<https://doi.org/10.1007/s00210-020-02013-x>

ORIGINAL ARTICLE

Fractalkine (CX3CL1) and Its Receptor CX3CR1: A Promising Therapeutic Target in Chronic Kidney Disease?

Sarah Cormican^{1,2} and Matthew D. Griffin^{1,2*}
¹Regenerative Medical Institute (REMEDI) at CURAM Centre for Research in Medical Devices, School of Medicine, College of Medicine, Nursing and Health Sciences, National University of Ireland, Galway, Ireland, ²Neurology, School of University Hospitals, Dublin University Health Group, Dublin, Ireland

Chronic treatment with the (iso-)glutaminyl cyclase inhibitor PQ529 is a novel and effective approach for glomerulonephritis in chronic kidney disease

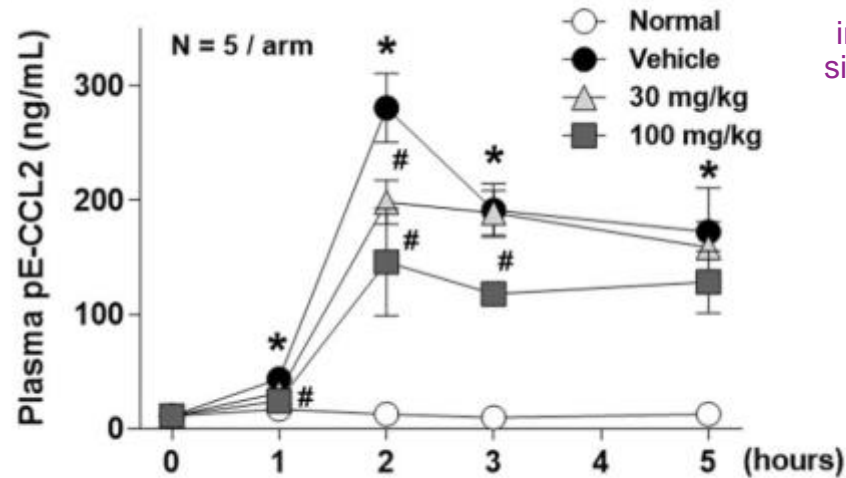
Naotoshi Kanemitsu¹, Fumiko Kiyonaga², Kazuhiko Mizukami³, Kyoichi Maeno³, Takashi Nishikubo⁴, Hiroyuki Yoshida³, Hiroyuki Ito³



QPCT/L inhibition with PQ529 shows reduction of inflammatory cytokines and improvement of kidney function in a rat glomerulonephritis model

Dose-dependent suppression in pE-CCL2 levels

- ◆ Following 3 weeks of repeated administration of PQ529 (30 and 100 mg/kg)



inflammatory signal reduced

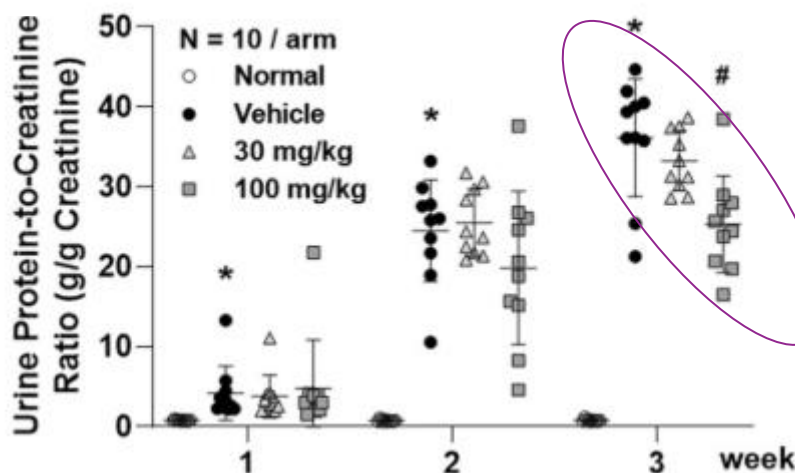


Kidney function improved



Dose-dependent reduction in protein excretion

- ◆ PQ529 (30 and 100 mg/kg) ameliorated the elevated urinary protein excretion (UACR) at week 3



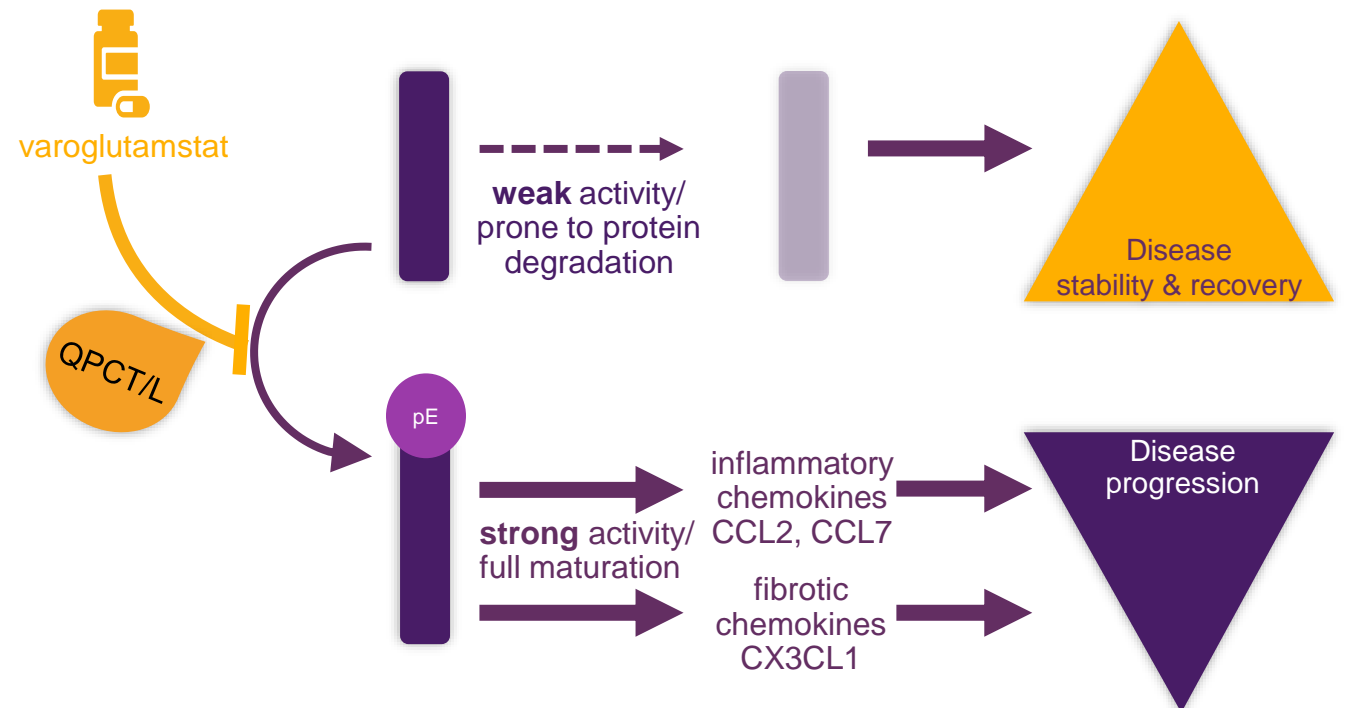
urine protein levels reduced



VIVIAD exploratory endpoint analyzing kidney function founded in scientific rationale

- ◆ Based on the known anti-inflammatory activity of varoglutamstat, VIVIAD protocol included investigation of kidney function and measurement of biomarkers of kidney inflammation and fibrosis to explore the role of QPCT/L inhibition on kidney function
- ◆ Although patients in VIVIAD were selected for their AD status and not for their kidney function level, many of them have reduced kidney function due to age and or comorbidities like type 2 diabetes or hypertension

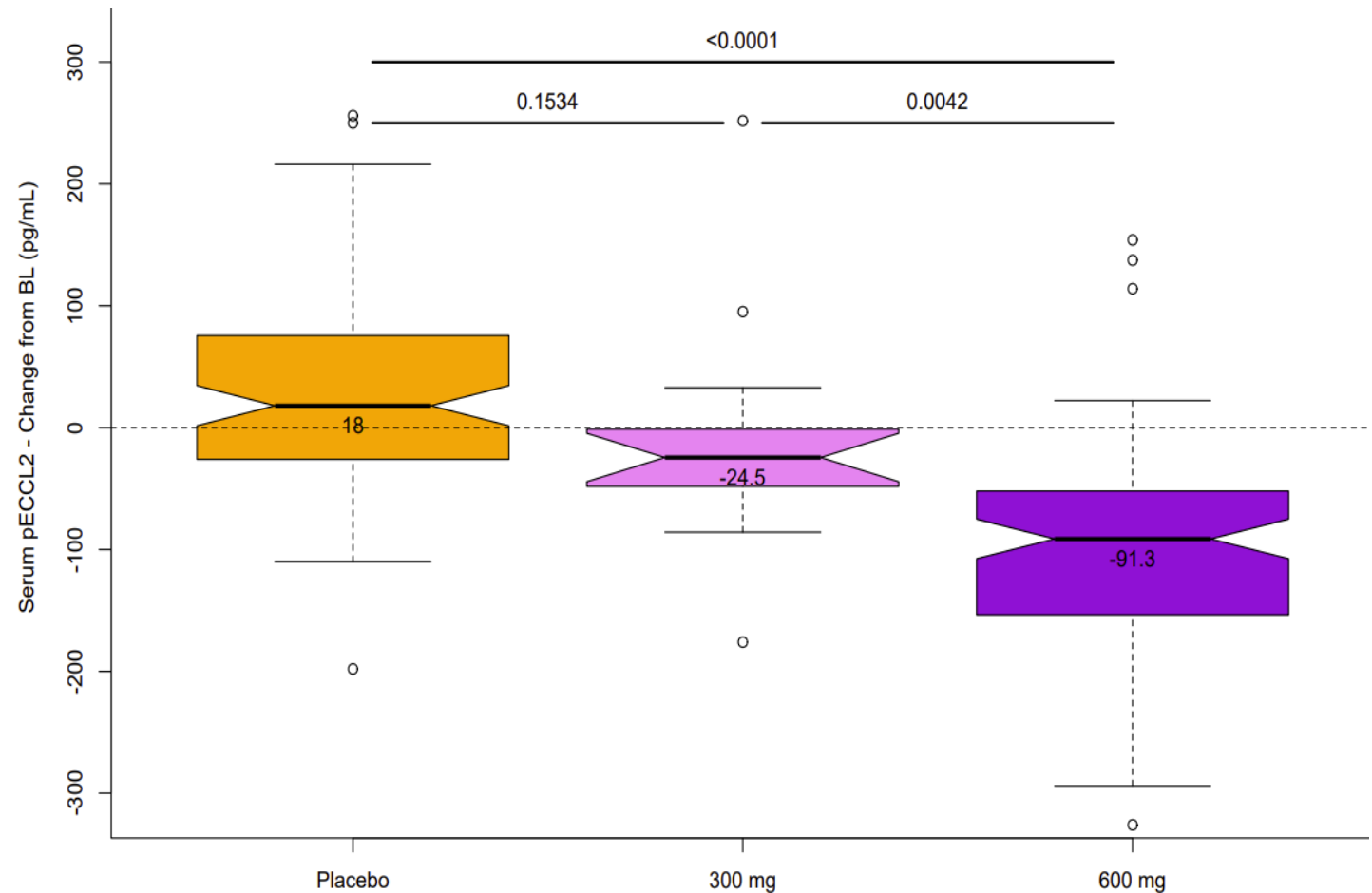
Varoglutamstat: Modulation of fibrotic and inflammatory processes on multiple layers



Varoglutamstat's potential role in modifying inflammatory pathways demonstrated by significant reduction in pE-CCL2 levels in VIVIAD patients

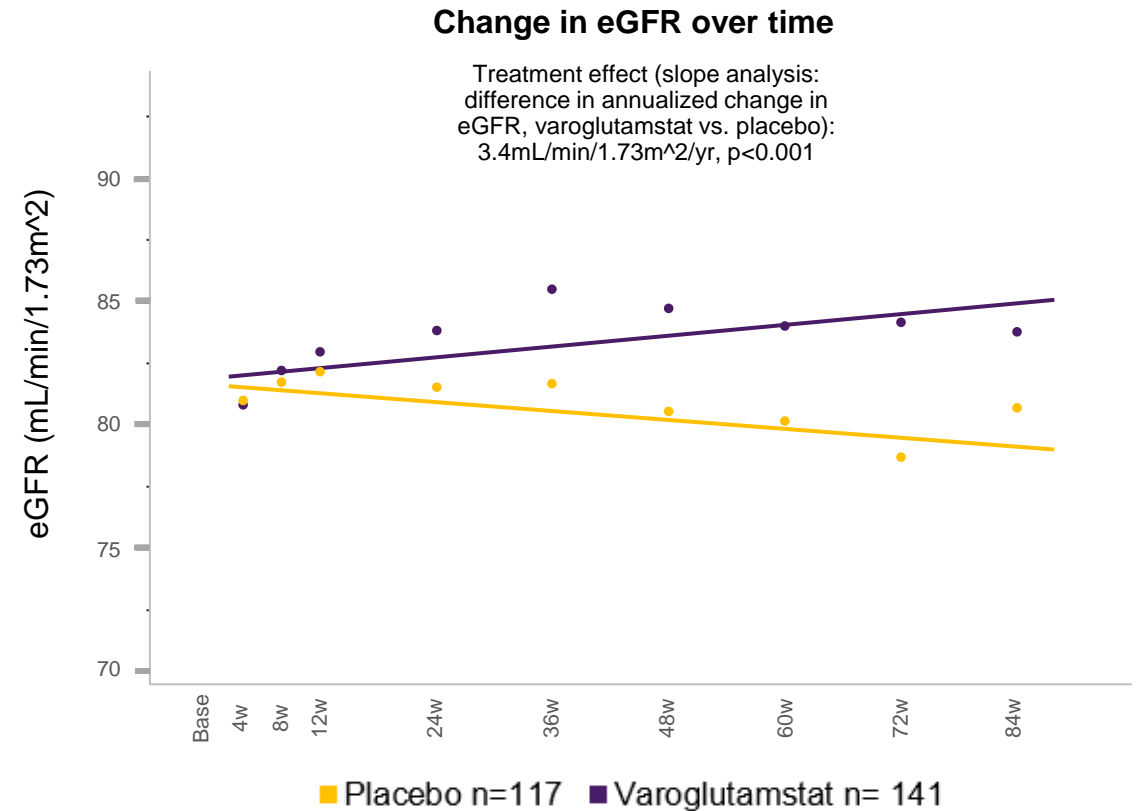
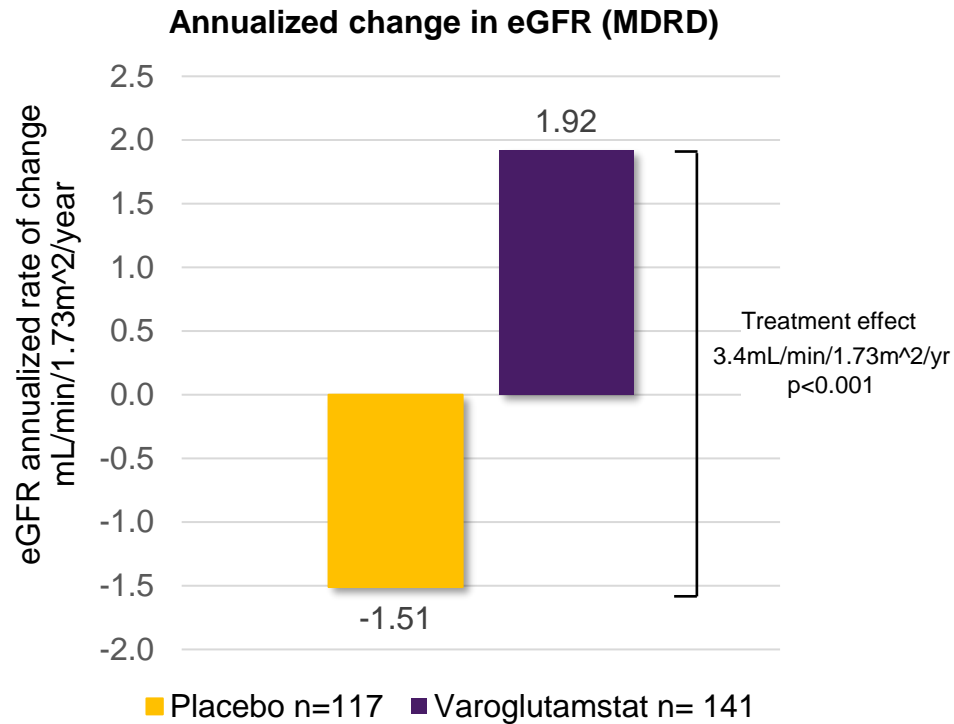
Change from baseline in serum pE-CCL2 levels at week 48

- ◆ Analysis of serum samples from VIVIAD study showed statistically significant dose-dependent decrease of pE-CCL2 levels with varoglutamstat at 600mg ($p < 0.0001$)

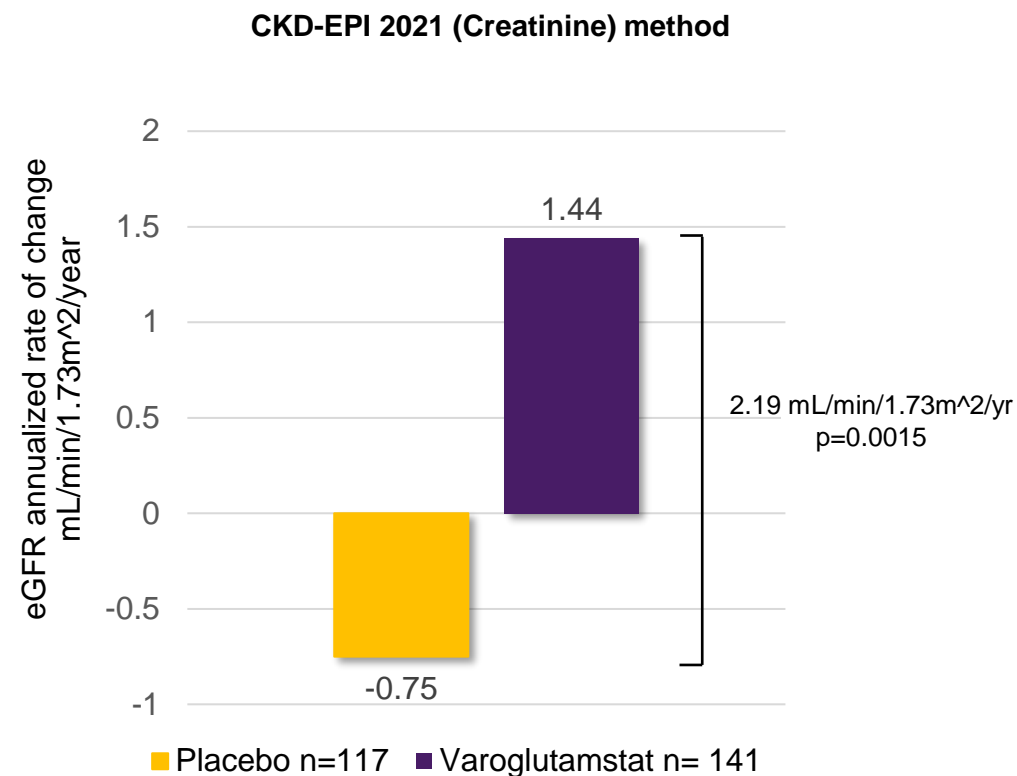
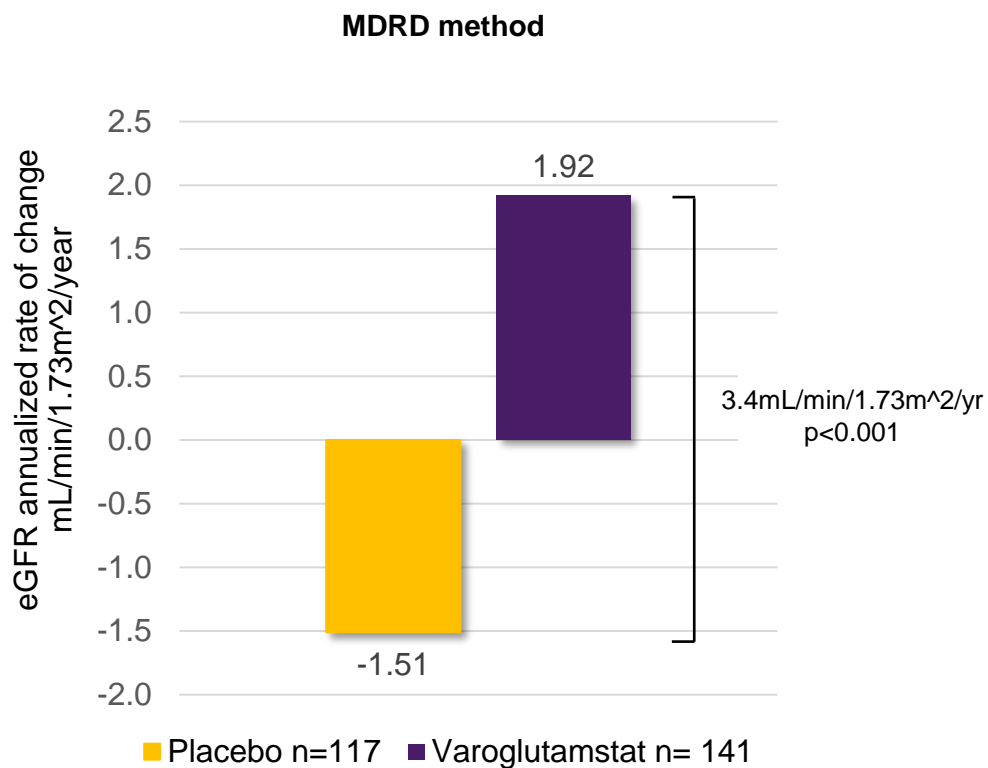


Statistically significant and clinically meaningful improvement in kidney function measured by eGFR (slope analysis; total VIVIAD population)

Sustained improvement in estimated glomerular filtration rate (eGFR) – a primary endpoint in many development programs of kidney disorders

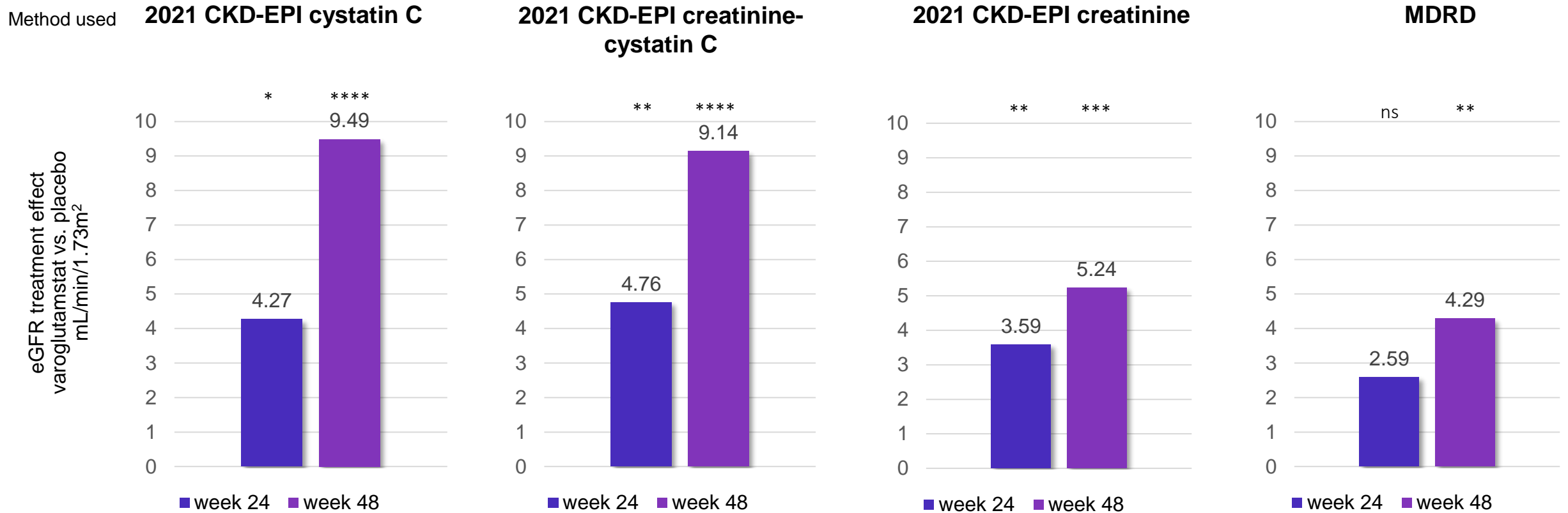


Improvement in eGFR was consistent between MDRD and CKD-EPI 2021 calculations for eGFR (slope analysis)



Consistency of results and effect size using a set of diverse and validated methods for eGFR assessment

Sensitivity analysis: baseline adjusted treatment effect of varoglutamstat versus placebo



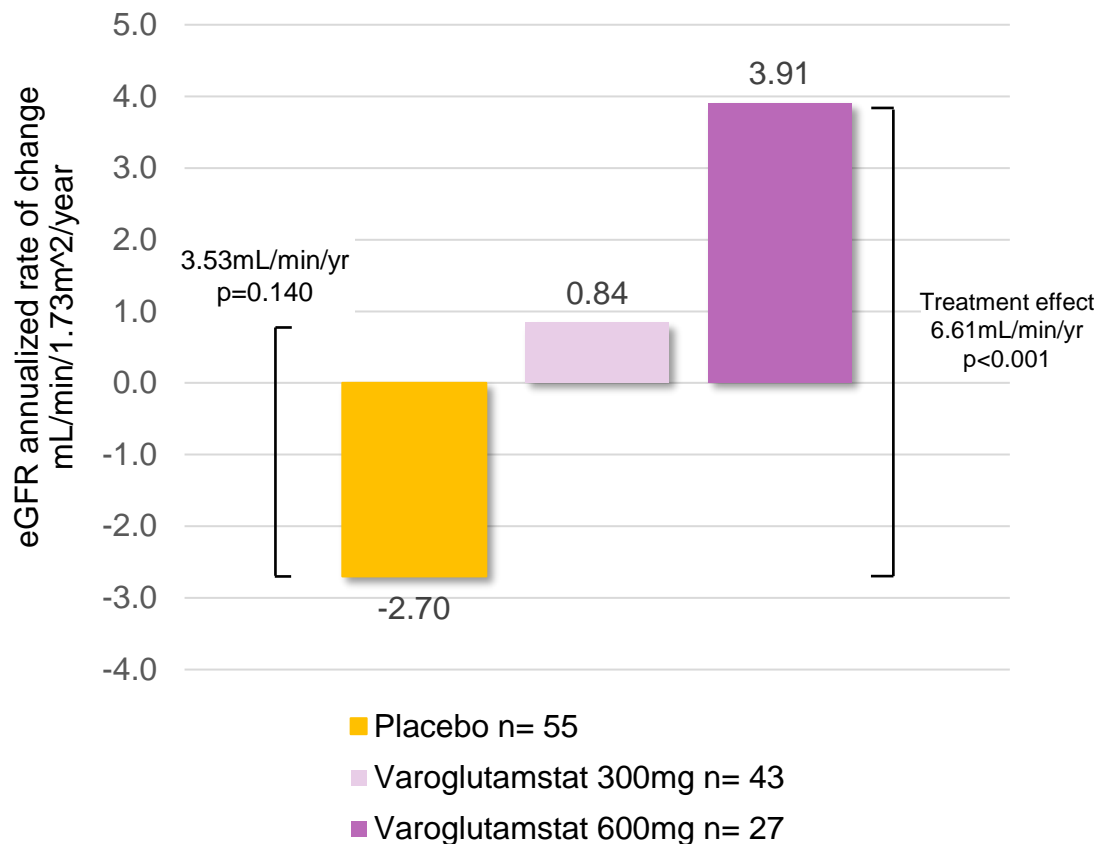
* significant difference (with p<0.05) ** significant difference (with p<0.01) *** significant difference (with p<0.001) **** significant difference (with p<0.0001)



Statistically significant and clinically meaningful effect in patients with risk factors for CKD defined as type 2 diabetes or hypertension

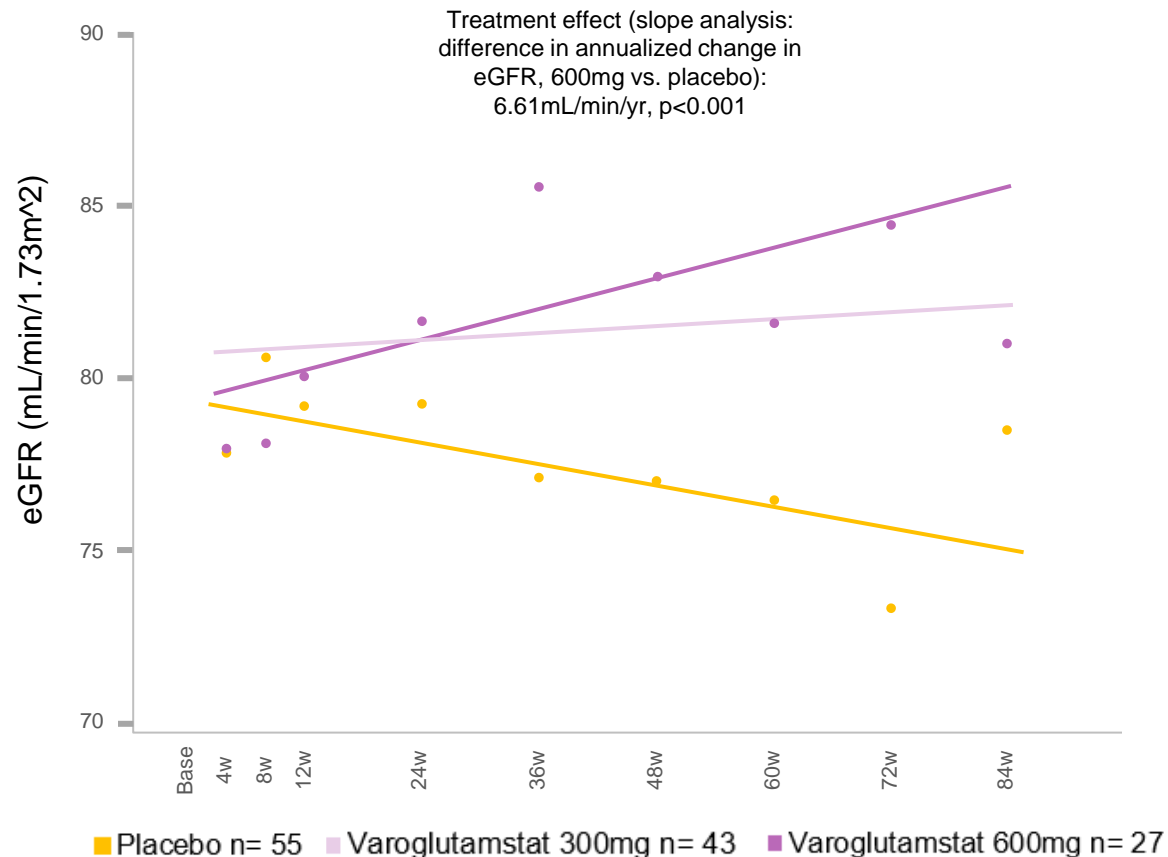
Varoglutamstat effect on eGFR in patients with risk factors

Annualized change in eGFR (MDRD) in subjects with risk factors



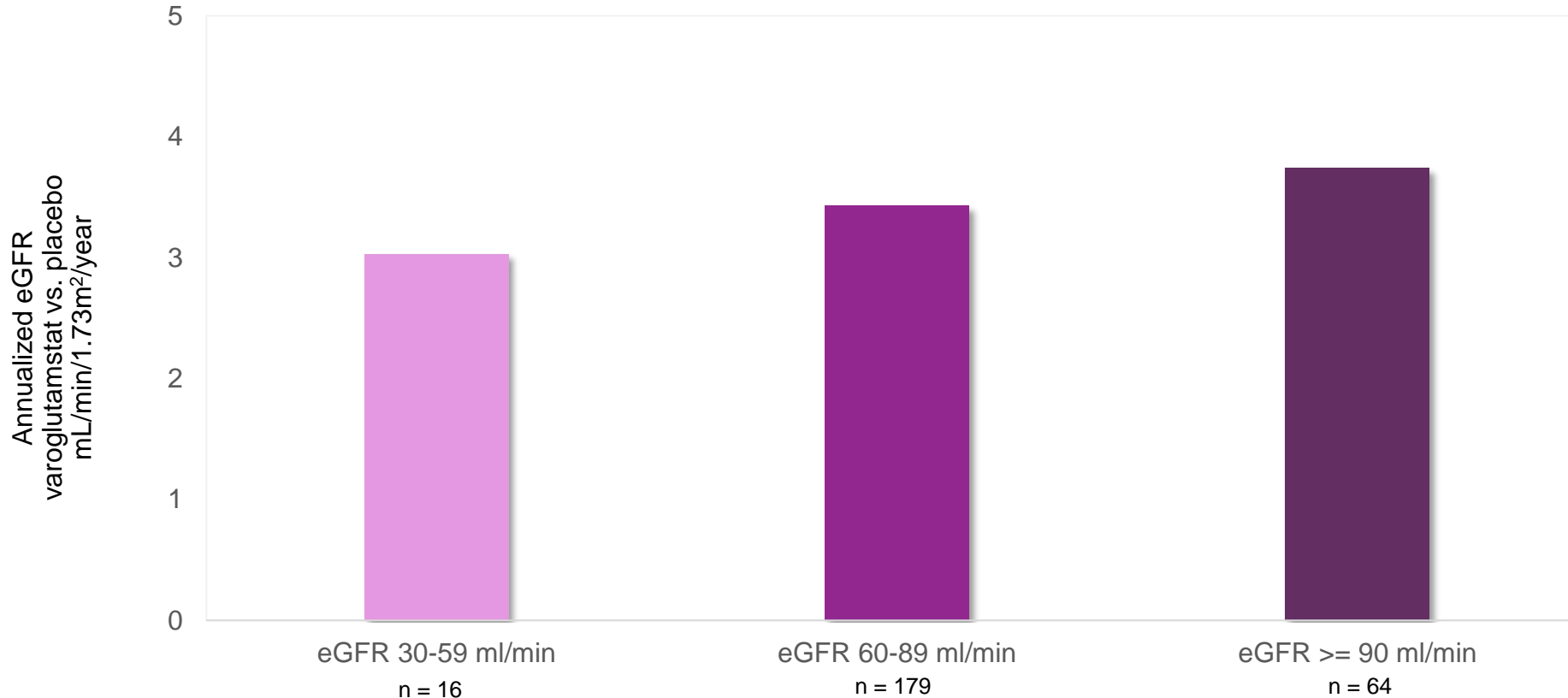
300mg and 600mg cohorts defined as randomized

Change in eGFR over time*



Effect of varoglutamstat on eGFR was also consistent across eGFR impairment level at baseline

Varoglutamstat annualized change of eGFR versus placebo



Robust proof-of-concept data demonstrating improvement of kidney function with QPCT/L inhibitors supports further evaluation of varoglutamstat in kidney disease

	Study	Biomarker	Kidney Function	Safety
Pre-clinical data ✓	◆ Rat Animal Model ¹ - PQ529	◆ Dose-dependent reduction of pE-CCL2	◆ Dose-dependent improvement of kidney function and proteinuria	◆ Good safety profile with no dose limiting toxicity observed
Clinical PoC ✓	◆ VIVIAD Human Data - varoglutamstat (PQ912)	◆ Dose-dependent reduction of pE-CCL2	◆ Dose-dependent improvement in kidney function as measured by eGFR over 2 years	◆ Good safety profile with no dose limiting safety findings observed



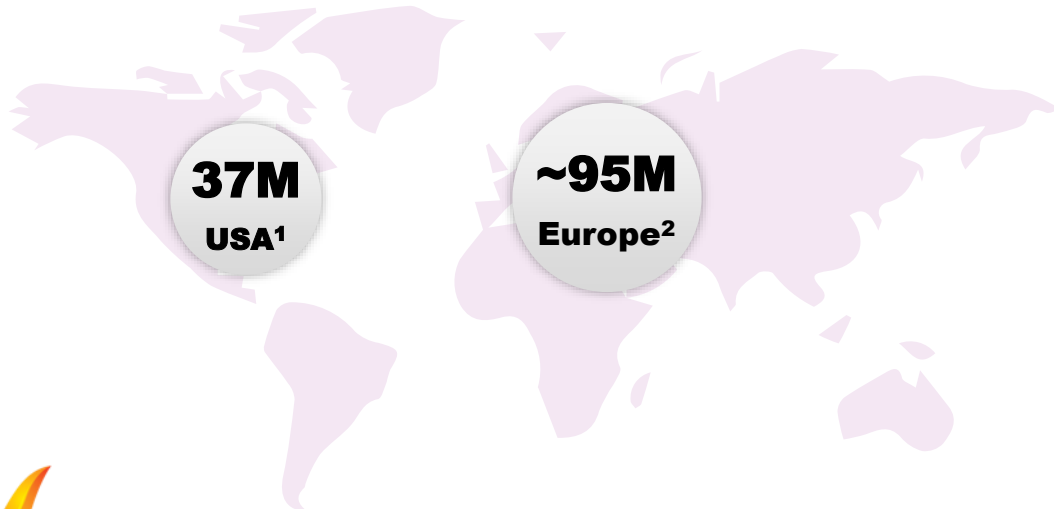
Addressing kidney disease is a rising global health imperative with high unmet needs

High prevalence

Global prevalence increasing, driven by a **growing and ageing** population and increase in diabetes, heart disease and hypertension

1 in 3 adults with diabetes may have CKD¹

1 in 5 adults with high blood pressure may have CKD¹



Increasing mortality

3rd fastest-growing cause of death³

5th highest cause of years of life lost by 2040³

15–20% of patients die within 12 months of starting dialysis in high-income countries³

High financial burden

~\$90K annual cost of hemodialysis patient per year in the U.S. (Medicare)¹

>\$120 billion annual cost of treating U.S. Medicare patients with CKD and/or end-stage renal disease (ESRD)⁴



Varoglutamstat potential in large indications – e.g. chronic kidney disease (CKD)

CKD is marked by a slow progressive decline in kidney function, often leading to kidney failure

There remains a high unmet need for new treatment options for patients

				Persistent albuminuria categories		
				Description and range		
				Normal to mildly increased	Moderately increased	Severely increased
				<30mg/g <3mg/mmol	30 - 300mg/g 3-30 mg/mmol	>300mg/g >30mg/mmol
				A1	A2	A3
GFR categories (ml/min/1.73m ²) range and description	>90	Normal and high	Stage 1	No CKD in absence of markers of kidney damage		
	60 - 89	Mild decrease related to normal age range	Stage 2			
	45 - 59	Mild - moderate reduction	Stage 3a			
	30 - 44	Moderate - severe reduction	Stage 3b			
	15 - 29	Severe reduction	Stage 4			
	< 15	Kidney failure	Stage 5			

Increasing risk

Increasing risk

Need

- ◆ Kidney function continues to decline despite introduction of new therapies to slow progression

Opportunity

- ◆ Varoglutamstat has potential to stabilize kidney function and reduce risk of disease progression to ESRD
- ◆ Initial target late-stage CKD (stage 3b/4) on top of SoC
 - ◆ 0.3-0.4 % of the population are estimated to have CKD stage 4, representing > 1 million people across U.S. and Europe¹
 - ◆ Selected high risk patients in CKD stage 3b provide additional opportunities

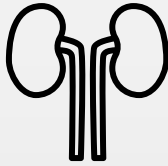
Potential path*

- ◆ Exploration in CKD could be achieved with a smaller study
- ◆ Registrational package would require large confirmatory studies e.g. 2 x Phase 2/3, >1500 pts; stage 3b/4 patients at high risk of progression on top of SoC; 5+ years to enroll and complete studies




Varoglutamstat potential in orphan diseases – e.g. Alport Syndrome


Alport Syndrome
Caused by x-linked genetic mutations in collagen IV genes




Progressive decline in kidney function leading to failure




Hearing loss



Vision problems



High blood pressure



There remains a high unmet need for new treatment options for people with Alport Syndrome

Need

- ◆ No specific treatment available; current therapies slow but do not prevent progression of kidney impairment

Opportunity

- ◆ Varoglutamstat has potential to stabilize kidney function and reduce risk of disease progression to ESRD
- ◆ ~ 150,000 patients in US and EU with moderate to high risk of kidney failure¹

Potential path*

- ◆ Faster time to market than larger indications such as CKD
- ◆ e.g. Phase 2/3, 180 pts; integrated design with interim readouts; ~4 years from enrollment to final results



Varoglutamstat has the potential to be the first QPCT/L inhibitor to improve kidney function in people with kidney disorders

First-in-class
QPCT/L inhibitor

Broad potential opportunity in CKD, orphan kidney diseases and other inflammatory and fibrotic diseases

Promising PoC data in patients at high risk of kidney disease

Full rights in US/Europe held by Vivoryon

Follow-on compounds in pre-clinical development

Extensive safety dataset (> 400 subjects exposed in Ph1 and Ph2 studies in early AD up to 800mg BID)



VIVIAD kidney function data informs priorities for varoglutamstat in 2024 and beyond, shaping clinical development path decisions and goals in kidney disease

Status

Compelling evidence achieved

- ✓ Statistically significant improvement in eGFR (total population and in patients at high-risk kidney disease)
- ✓ Evidence of dose response
- ✓ Consistent effect across range of eGFR impairment at baseline
- ✓ Robust safety data set in elderly patient population

Next Step

Decide clinical path / indications

Main clinical development goals

- ◆ Effect size in CKD stage 4 and/or orphan kidney disorders
- ◆ Effect on albuminuria
- ◆ Sustained efficacy post discontinuation of treatment
- ◆ Reduce event rate to ESRD

Supportive data package

- ◆ Conduct additional biomarker analyses
- ◆ Continue to investigate MOA and QPCT/L pathway interactions in target indications



50%

Nam id diam eget nisi. Quis tempus id
condimentum eget vitae. Quis tempus id
viti eget vehicula. Morbi id justo vehicula,
consequat magna placerat, lacus massa.
Maecenas ut amet nunc a mi tempus portitor
vel vitae nisi. Etiam auctor leo ut amet lectus
luctus, vel sagittis mi fermentum. Curabitur ut
vehicula arcu. Sed sed tortor mi. Maecenas
nec fronsit ante. Duis a vestibulum nisi.
Suspendisse portitor nulla et egestas facilis.
Maecenas id lacina ex, id portitor est.

Duis a odio sed mauris egestas ornare at a
est. Sed pharetra, nisi a ultrices sed velit.
quam enim elefero nulla, nec condimentum

2008	2009	2010	2011	2012	2013	2014	2015	2016
33.29	28.92	17.25	1.11	16.53	33.63	12.64	0.48	12.77
37.04	28.76	17.28	1.08	16.44	33.61	12.58	0.40	12.68



FINANCIAL RESULTS



Key financial figures

In €k	Mar 31, 2024	Mar 31, 2023
Revenue	0	0
Research & Development expenses	(7,425)	(3,104)
General & Administrative expenses	(2,084)	(1,906)
Net loss for the period	(9,329)	(5,110)

In €k	Mar 31, 2024	Dec 31, 2023
Cash & cash equivalents	21,994	18,562*
Financial assets	0	10,165*

Cash runway into Q2 2025

Further funding and/or partnerships required to support potential additional clinical studies and/or to extend runway beyond Q2 2025





OUTLOOK & STRATEGIC PRIORITIES

Strong kidney data reinforce strategic shift to inflammation and fibrosis-driven kidney indications and are a further step towards securing Company's future

Pursue actionable plan to establish presence in kidney disease

- ◆ Rigorous scientific research laid foundation for opportunity in kidney disease despite AD setbacks
- ◆ Decide on clinical development pathway
 - ◆ Sharpen clinical stage plans in CKD and/or orphan kidney diseases
 - ◆ Enhance dataset of varoglutamstat in kidney disease
- ◆ Build presence with scientific / medical advisors in nephrology community

Complete Phase 2 AD program, explore select early stage programs

- ◆ Topline VIVA-MIND study results expected end 2024 to inform next steps in early AD
- ◆ Focus on most promising QPCT/L inhibitors in inflammatory / fibrotic disorders
- ◆ Assess potential of meprin inhibitors and mAb

Corporate focus on prudent cash runway management and funding/BD

- ◆ Cash runway into Q2 2025*
- ◆ Actively pursue funding / business development to support efforts in kidney disease and beyond
- ◆ Highly dedicated team in place to drive transformation





Q&A

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